

## Enzyme rhythms in model ox\_red\_2

Model name: ox\_red\_2

### o Optimisation problem

- Protein turnover time  $1.8e+03$  s = 30 min
- Perturbed parameter(s) : S
- Perturbation frequency  $f$  : 1/s (period 1 s)
- Scored quantity: red
- Scored quantity: ox
- Scored quantity: prod
- Fitness-averaged fitness
- Posttranslational rhythms allowed
- Standard frequency considered  $f$  : 1/s (period 1 s)

### o Model properties:

- inactive\_enzymes: 0
- balanced\_reference\_state: 1
- consider\_external\_rhythm: 1
- adaptive\_rhythm: 1
- spontaneous\_rhythm: 0
- spontaneous\_rhythm\_at\_omega: 0
- has\_spontaneous\_rhythm\_and\_inactive\_enzymes: 0

### o No beneficial self-induced oscillation found

### o Fitness changes after external perturbation at frequency $f=1/s$

- Change by perturbation alone (xx): -0.0106
- Change by adaption synergies (xu): 0.00594
- Change by periodic enzyme (uu): -0.0109
- Change by enzyme mean shift (u): -1.79e-08
- Total fitness change : -0.0155
- Fitness gain by adaption : -0.00494
- Maximum adaptive fitness found (in tested range) at frequency  $f=0.178/s$  (period 5.62 s)
- Predicted max. fitness change (adaptive, num. opt, full ampl. constraints) at frequency  $f=0.178$ : -0.0132

### o Self-induced oscillations?

- No beneficial self-induced oscillations (2nd order, amplitude below 1/2 of mean) found at frequency  $f = 1/s$  (principal synergy = -0.531): Predicted fitness change -0.0422

### o Numerical calculation (responsive, $f=1$ )

- Fitness change (fitness-averaged): -0.0106
- Fitness change (state-averaged): -8.96e-05

### o Numerical calculation (adaptive, $f=1$ )

- Fitness change (fitness-averaged): -0.0076
- Fitness change (state-averaged): 0.0129

### o Numerical calculation (self-induced rhythm, amplitude below 1/2 of mean, $f=1$ )

- Fitness change (fitness-averaged) : 9.99e-06
- Fitness change (state-averaged): 9.99e-06

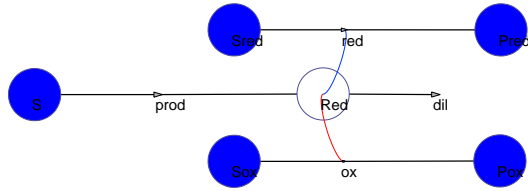


Figure 1: Network and reference flux

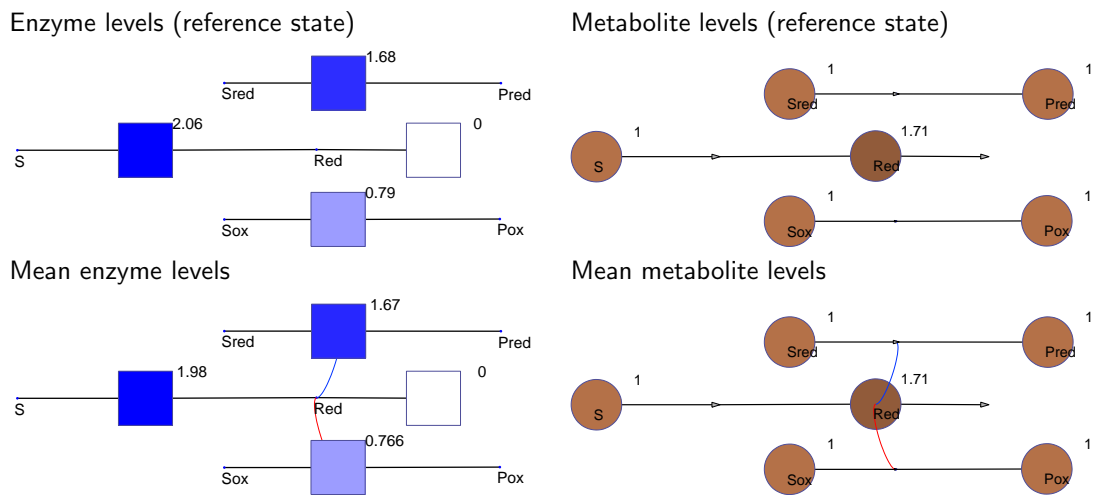
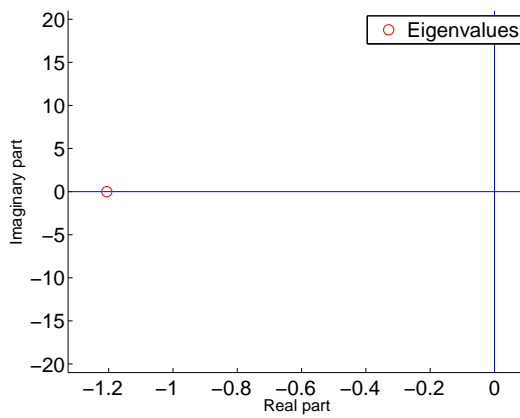
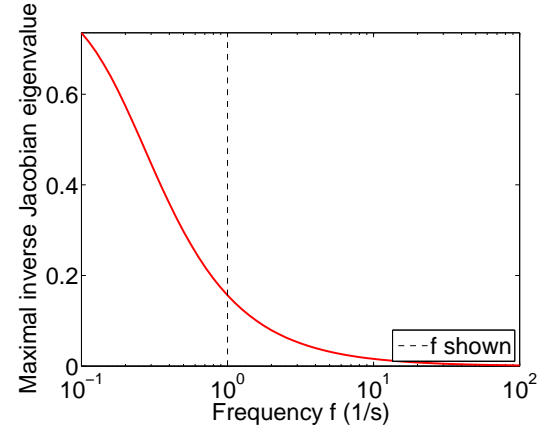


Figure 2: Reference state (top) and mean state during oscillation (bottom).

Jacobian eigenvalues at reference state



Maximal inverse absolute Jacobian eigenvalue



Principal synergy  $\sigma$

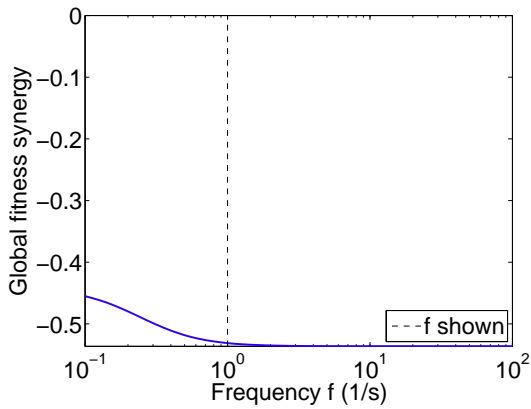
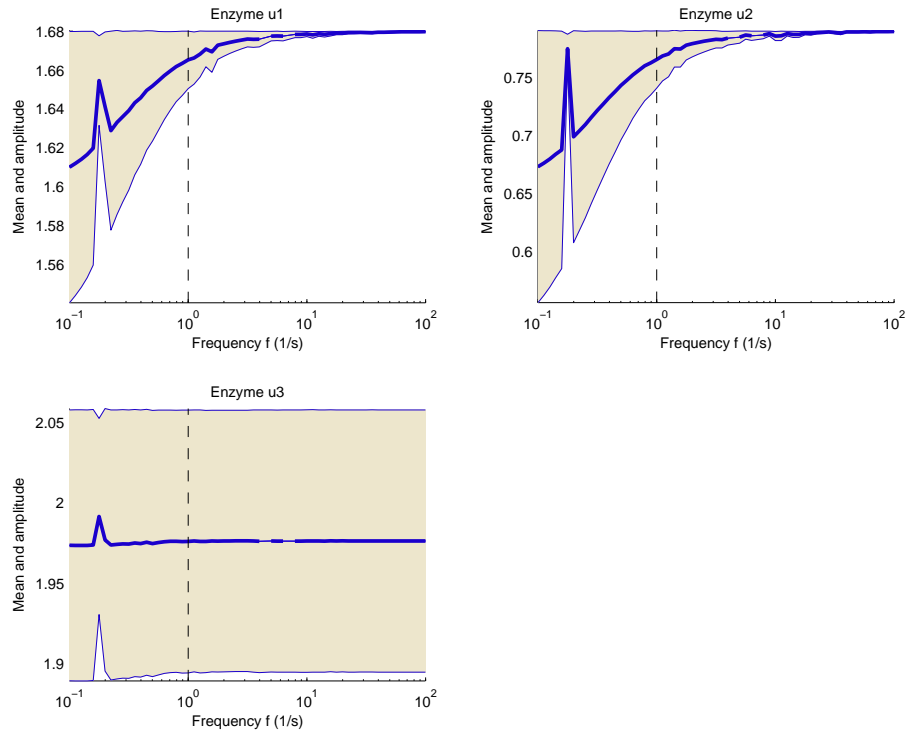
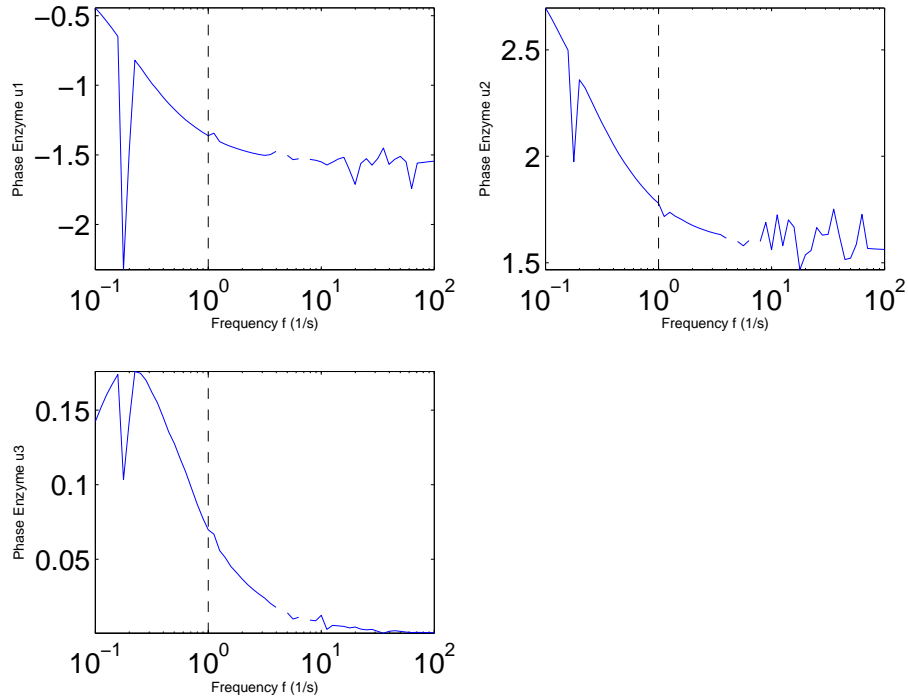


Figure 3: Control analysis. Left: Global fitness synergy (maximal fitness curvature eigenvalue), as a function of the frequency. Right: Relative amplitudes of individual enzymes for the least wasteful enzyme mode (components of the leading fitness curvature eigenvector).

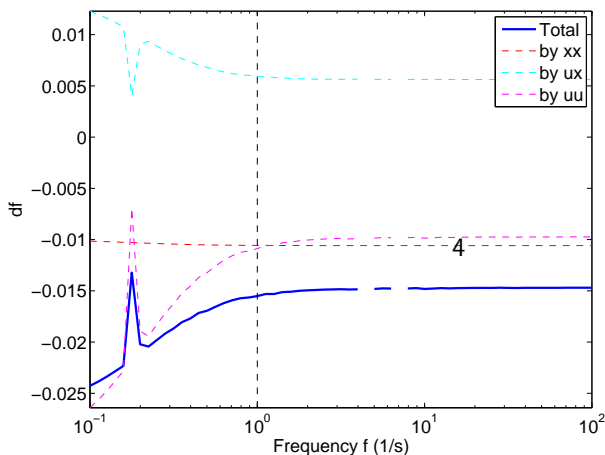
Protein level and enzyme activity (mean and amplitude)



Phase angles  $[0, 2\pi]$



Fitness change



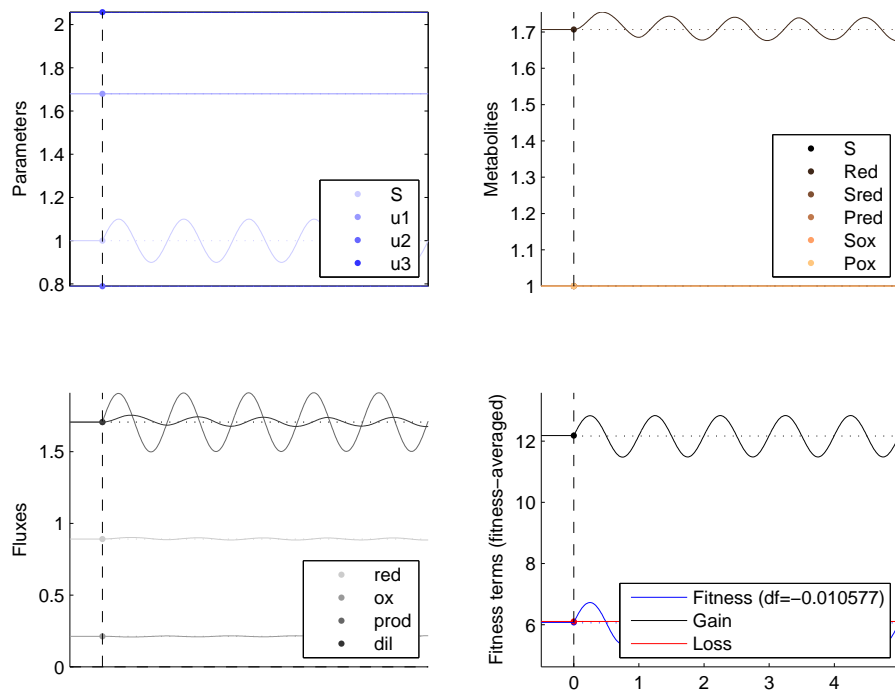


Figure 5: Numerical calculations: responsive oscillations (curves). Dynamic effects of oscillations. The panels show different types of variables: (i) Optimal periodic enzyme levels; (ii) internal metabolite levels; (iii) reaction fluxes; (iv) fitness, benefit, and cost. Perturbation frequency see first page.

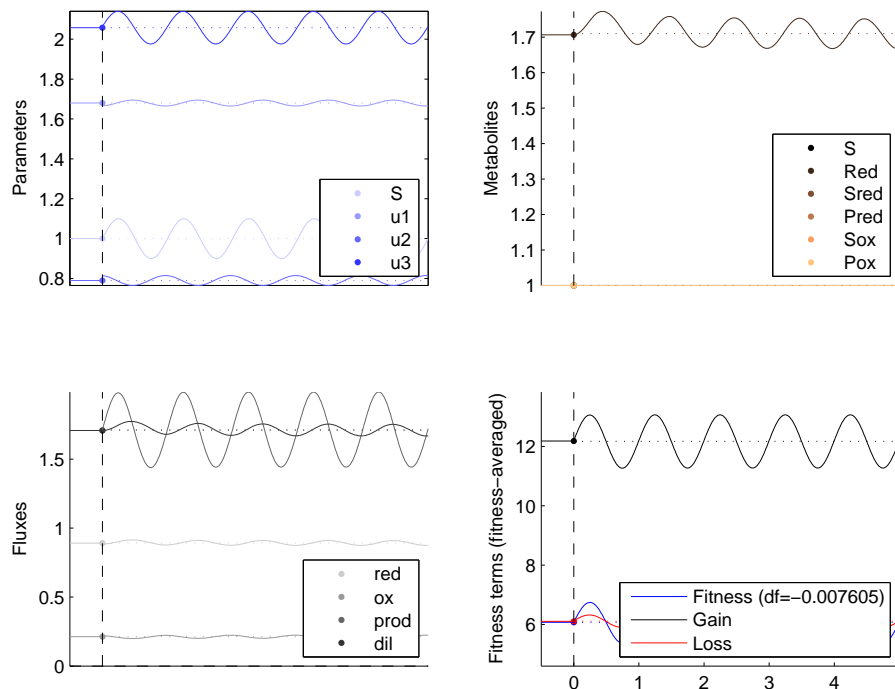
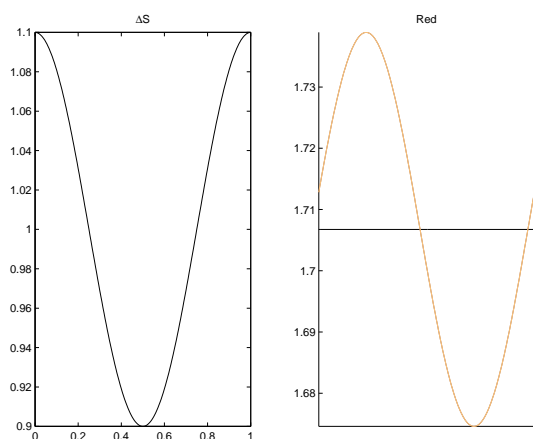
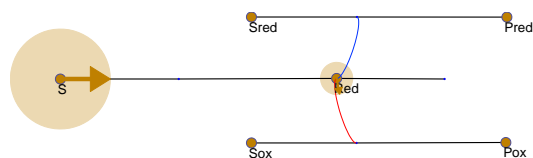


Figure 6: Numerical calculations: adaptive oscillations (curves). Dynamic effects of oscillations. The panels show different types of variables: (i) Optimal periodic enzyme levels; (ii) internal metabolite levels; (iii) reaction fluxes; (iv) fitness, benefit, and cost. Perturbation frequency see first page.

Responsive oscillations (concentrations)



Responsive oscillations (fluxes)

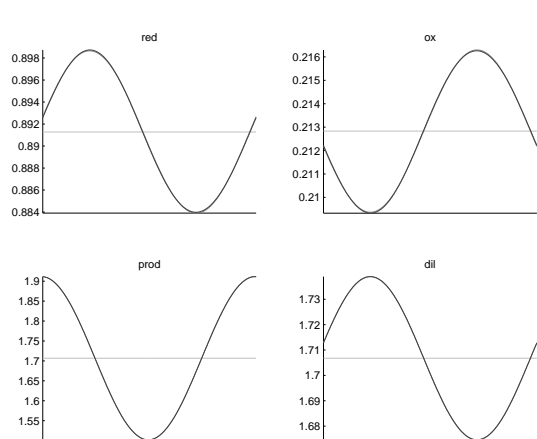
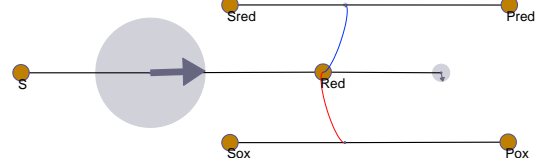
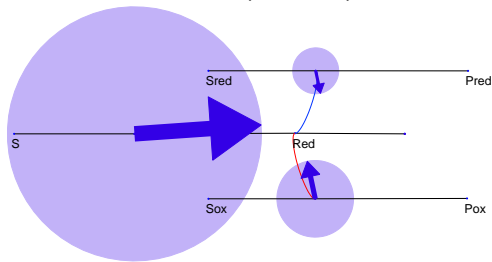
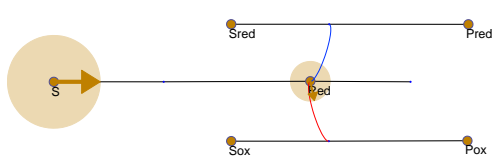


Figure 7: Responsive oscillations (local expansion; arrows: absolute changes) Perturbation frequency see first page.

### Adaptive oscillations (enzymes)



### Adaptive oscillations (metabolites)



### Adaptive oscillations (fluxes)

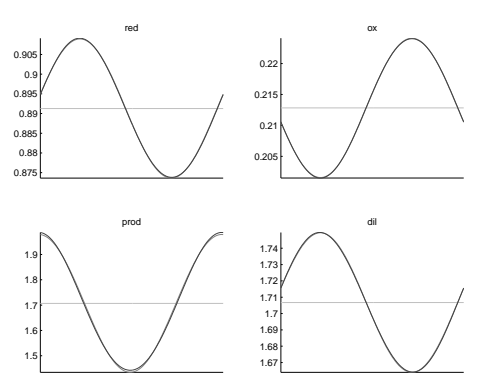
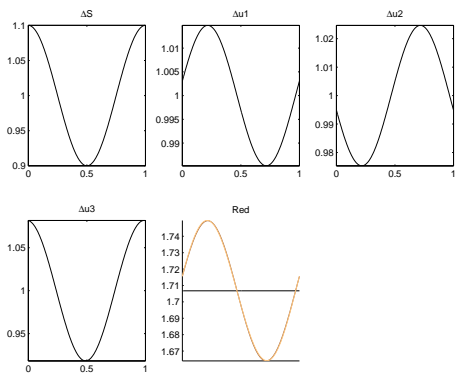
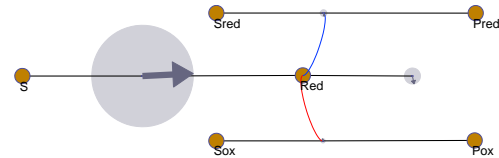


Figure 8: Adaption to forced oscillations (local expansion; arrows: absolute changes). Perturbation frequency see first page.

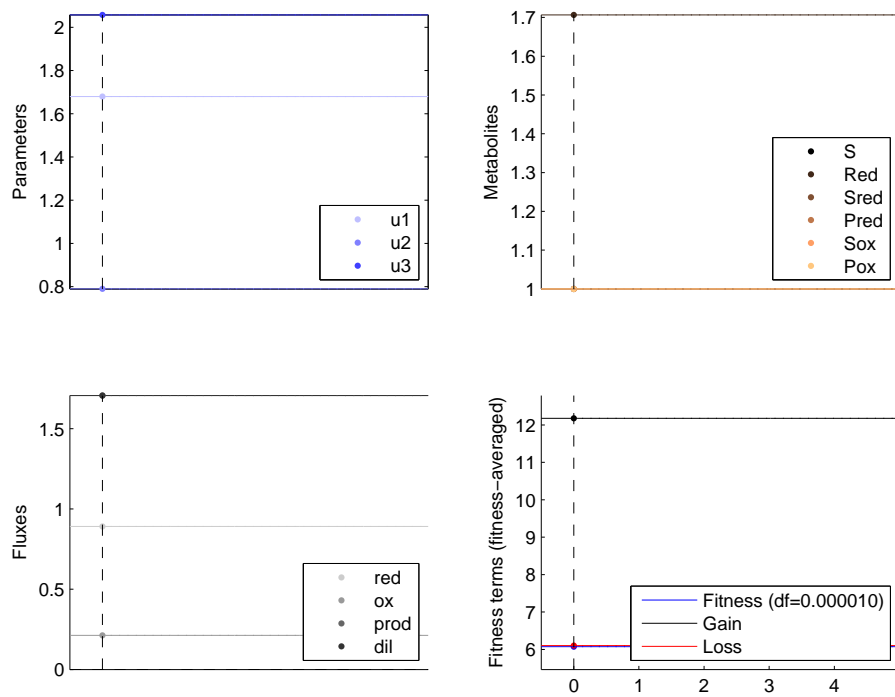
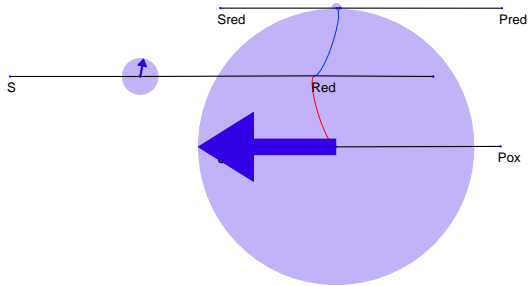


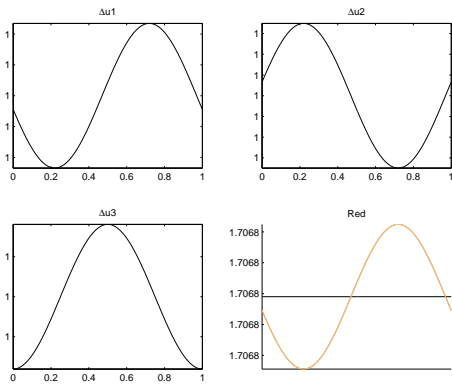
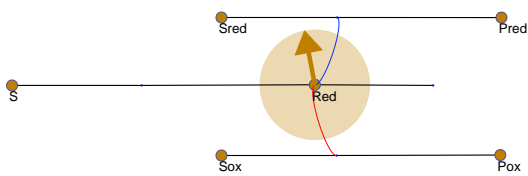
Figure 9: Tentative spontaneous oscillations. Perturbation frequency see first page.



### Enzyme rhythm



### Spontaneous oscillations (concentrations)



### Spontaneous oscillations (fluxes)

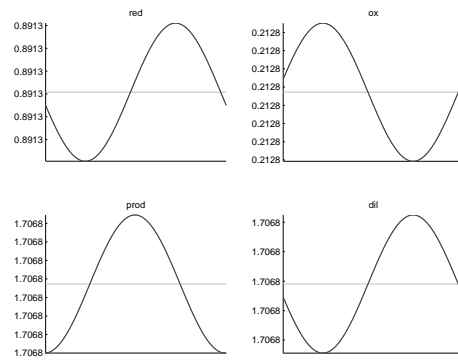
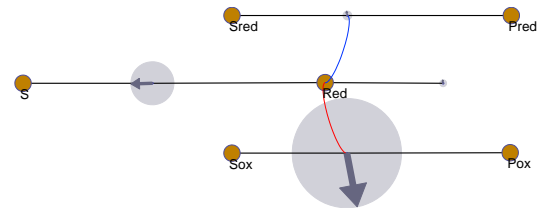
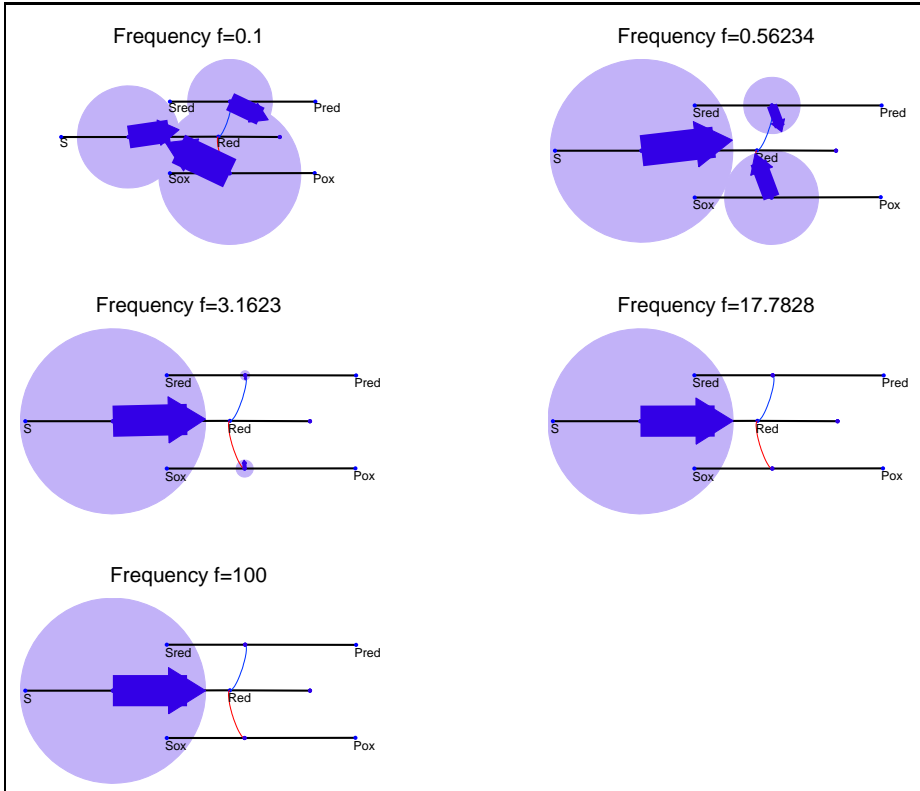


Figure 10: Tentative spontaneous oscillations (local expansion; arrows: absolute changes). Perturbation frequency see first page.

Adaptive



Least costly spontaneous

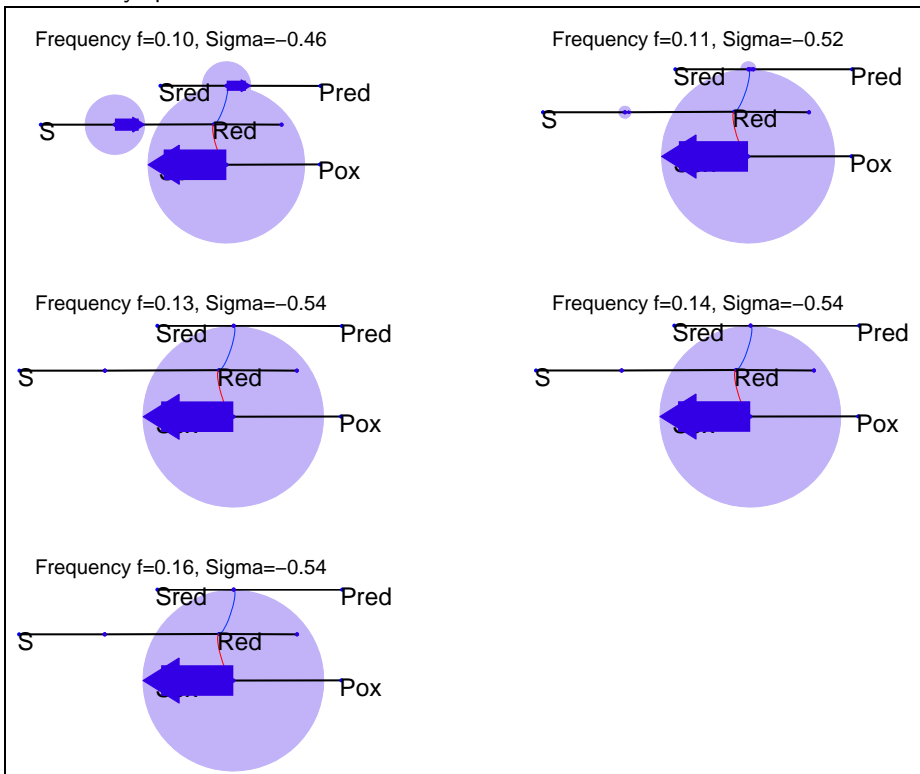


Figure 11: Potential oscillations at various frequencies (local expansion).